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Commentary

Commentary: Despite reports of catastrophic complications, why recombinant human bone morphogenetic protein-2 should be available for use in anterior cervical spine surgery

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COMMENTARY ON: Woo EJ. Recombinant human bone morphogenetic protein-2: adverse events reported to the Manufacturer and User Facility Device Experience database. Spine J 2012;12:894–9 (*in this issue*).

The Food and Drug Administration (FDA) first issued their warnings about life-threatening complications associated with the usage of recombinant human bone morphogenetic protein (rhBMP) in the anterior cervical spine on July 1, 2008. Despite this, rhBMP continues to be used in the cervical spine, and most disturbingly, catastrophic swelling, respiratory distress, and wound complications continue to be reported. In this issue of *The Spine Journal*, the FDA's Manufacturer and User Facility Device Experience database for rhBMP-2 is examined. Dr Woo [1] observes that despite the 2008 public health warning, ''one of the most striking (findings) is the continued reporting of these potentially life-threatening adverse events and the need for emergent intervention.''

If this were not enough bad news, there is recent data analysis from the FDA and others suggesting that high doses of rhBMP-2 (40 mg) used in the AMPLIFY trial were associated with an incidence of new cancer events. By 30 months postoperatively, a five to sevenfold higher rate of cancers was seen after rhBMP-2 exposure compared with the controls. A potential mechanism for this observation is that, although rhBMP-2 may not be carcinogenic in this early time frame, the potent growth factor may be a promoter of subclinical cancers. That is, rhBMP-2 exposure may affect already existing subclinical disease, making the cancer cells grow faster or transform to greater invasiveness, becoming clinically apparent malignancies [2,3].

As both of these observed complications associated with rhBMP-2 can be life-threatening, some have viewed these findings as a call to remove rhBMP-2 from the market, or perhaps ban the use specifically in the cervical spine. We disagree. Although rhBMP can cause catastrophic complications, it is also the most powerful inducer of bone formation available commercially. We believe that judicious use of appropriate doses, in special cases, should remain an option for surgeons and well-informed patients.

How can we justify such a position in light of the fact that this is a potentially life-threatening product used for a nonlife-threatening problem, especially when there are viable alternatives? As clinicians, we are well aware that virtually every therapeutic decision we make in medicine involves an assessment of the risks versus the benefits.

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For example, although acetaminophen is widely perceived to be a safe and an effective medication, according to one article, ''Acetaminophen overdose is the leading cause for calls to Poison Control Centers (>100,000/y) and accounts for more than 56,000 emergency room visits, 2,600 hospitalizations, and an estimated 458 deaths due to acute liver failure each year'' [4]. Yet, the FDA, appropriately, has no plans to consider banning the use of acetaminophen.

To be clear, the overwhelming majority of cervical fusion cases do not require rhBMP. However, like any other potentially dangerous drug with some beneficial effect, we believe rhBMP-2 can have its uses. For example, if a patient with multiple comorbidities associated with an increased risk for pseudarthrosis requires a multilevel cervical arthrodesis, one can do an anteroposterior operation to increase the rate of solid fusion. Alternatively, one could accept the risk of pseudarthrosis, knowing that a reoperation may be necessary for some patients. But what if that patient has comorbidities that increase the risk of circumferential surgery or reoperation? In such cases, judicious use of rhBMP, at an appropriate dose, may in fact be the less dangerous alternative.

Bone morphogenetic protein is a naturally occurring substance that the body normally makes to heal bones, albeit at infinitesimally small levels. Trace amounts of it exist in the commercial demineralized bone matrix products. At such small doses, bone morphogenetic protein in demineralized bone matrix is not known to produce deleterious reactions. Unfortunately, it also does not induce bony healing at a reproducibly high rate. Therefore, it is obvious that minute doses do not appear to cause problems, whereas large doses result in a high incidence of complications. In theory, at least, there may exist an ideal dose at which bone healing is reproducibly enhanced, but the incidence and severity of adverse reactions are minimized.

For the past decade, the first author (KDR) has been using rhBMP in the cervical spine in patients with special needs for fusion augmentation. Initially, when high doses (1–3 mg/level) were used, retropharyngeal edema and fluid was common, although easily treated with steroids. Reoperations were rare and there were no deaths in my experience. More recently, we have most commonly used 0.2 to 0.4 mg per level. In addition, we place a small dose (20–40 mg) of a high-potency particulate steroid (eg, methylprednisolone) in the wound before closure. These patients anecdotally have less dysphagia than those in whom we do not use rhBMP because we do not routinely use steroids in those individuals. Although the fusion rate is not 100%, we have noted a much higher fusion rate for these high-risk patients than historical controls. We are in the process of determining if even lower doses can still be effective. We inform each patient about the FDA and American Academy of Orthopaedic Surgeons warnings (available at www.aaos.org). In addition, the risk of cancer is disclosed. Only if the patient is well informed and willing to sign a special consent, do we use the product.

In conclusion, we strongly believe that rhBMP-2 use should not be banned in the cervical spine. Rather, it should be used prudently in the small subset of patients for whom the risks of a failed surgery clearly outweigh the risks of very low-dose rhBMP-2 fusion augmentation. Surgeons and patients should understand that like many potent drugs, rhBMP is dangerous and only clinicians who are well informed about its potential catastrophic complications should use it. This caveat is particularly important in the anterior cervical spine.

We believe that patients can be appropriately informed of the risks involved and make reasonable decisions. Furthermore, patients *must* be well informed so that they can be alert to the signs of progressive retropharyngeal edema and how this effect may be delayed in presentation. Special care must be taken: the potential for life-threatening complications must be weighed against its possible benefits; the lowest possible doses should be used; and prudent patient care during the postoperative period, especially in the week or so after discharge, is essential.

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